

D2 3 70. The method of claim ~~65~~, wherein said reduction in said proteolytic products is determined by measuring the level of said proteolytic products in the nucleus of the cell.

4 71. The method of claim ~~65~~, wherein said reduction in said proteolytic products is determined by measuring the level of said proteolytic products in the cytoplasm of the cell.

#### REMARKS

Claims 65-71 are pending. Claims 65, 70 and 71 are amended herein.

#### Rejection of Claims 65-71 under 35 U.S.C. §112, first paragraph

Claims 65-71 were rejected, in the office action mailed July 5, 2001, under 35 U.S.C. §112, first paragraph for alleged failure to comply with the written description requirement.

The Examiner stated that there is no support for the phrase "wherein a reduction in the level of NFκβ proteolytic products" as recited in claim 65.

Applicants have amended claim 65 and dependent claims 66-71 to replace the phrase "NFκβ proteolytic products" with the phrase "proteolytic products derived from the proteolytic processing of NFκβ by said proteasomes".

Applicants submit that support for the phrase "proteolytic products derived from the proteolytic processing of NFκβ by said proteasomes" is found in the specification at p. 10, lines 10-20 wherein it is stated,

"[a]s used herein in reference to proteasome activity, the term 'reduction' refers to the failure of the proteasome to cleave a target ubiquitinated protein at as few as one-, more than one-, or even as many as all of the sites that it normally (i.e., in a genetically wild-type or otherwise healthy individual) recognizes and cleaves in that protein. Preferably such a reduction involves failure to cleave the target protein at 5-10% of sites, more preferably at 20-50% of sites, and most preferably at 75-100% of such sites."

The specification teaches the formation of proteolytic products derived from the proteolytic processing of NFκβ by a proteasome at p. 11, lines 14-16, wherein it is stated, "preferably, the reduction in proteasome activity comprises a reduction of proteolytic processing of NFκβ or a subunit thereof."

It is also stated at p. 42, line 28- p. 43, line 2, “[t]he kinase, in turn, phosphorylates the NFκβ inhibitor protein Iαβκ marking it for ubiquitination. In unstimulated cells, Iκβ binds to- and inhibits the activity of NFκβ. When ubiquitinated Iκβ is degraded by the proteasome, NFκβ translocates to the nucleus where it activates transcription.”

Applicants also submit that as of the filing date of the instant application it was known in the art that NFκβ is proteolytically processed via the proteasome pathway (see Palombella et al., 1994, Cell, 78: 773-85 (Exhibit A; Chen et al., 1995, Genes Dev., 9:1586-97 (Exhibit B); Li et al., 1995, Biochem. Biophys. Res. Commun., 215:292-301 (Exhibit C)).

In view of the above, Applicants submit that the specification clearly provides support for a “method of screening for autoimmune disease associated with a reduction in NFκβ activity in a mammal deemed to be at risk for an autoimmune disease, comprising: a) providing a biological sample from a mammal; and b) detecting activity of proteasomes in said sample by measuring the level of **proteolytic products derived from the proteolytic processing of NFκβ by said proteasomes** generated by said proteasomes, wherein a reduction in the level of said proteolytic products from a basal state is correlated with the presence of an autoimmune disease associated with a reduction in NFκβ activity,” as claimed in amended claim 65 and dependent claims 66-71.

In view of the above, Applicants respectfully request withdrawal of the 35 U.S.C. §112, first paragraph rejection of claims 65-71.

Rejection of claims 65-71 under 35 U.S.C. §112, second paragraph

Claims 65-71 were rejected, in the office action of July 5, 2001, under 35 U.S.C. §112, second paragraph for alleged indefiniteness.

The Examiner stated, “[i]n claims 65, 70 and 71, the phrase “NFκβ proteolytic products” is repugnant to the art recognized function of NFκβ, because NFκβ is not recognized to enzymatically cleave proteins”.

Applicants have amended claim 65 and dependent claims 66-71 to replace the phrase “NFκβ proteolytic products” with the phrase “proteolytic products derived from the proteolytic processing of NFκβ by said proteasomes”. Support for this amendment is discussed above in Applicants response to the 35 U.S.C. §112, first paragraph rejection of claims 65-71.

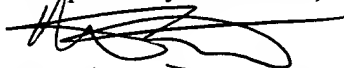
In view of the above, Applicants submit that the phrase "proteolytic products derived from the proteolytic processing of NF $\kappa$ B by said proteasomes" is not indefinite and respectfully requests withdrawal of the 35 U.S.C. §112, second paragraph rejection of claims 65-71.

Applicants submit that in view of the foregoing amendments and remarks, all issues relevant to patentability raised in the outstanding Office Action have been addressed. Applicants respectfully request reconsideration of the claims.

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Respectfully submitted,



Matthew Beaudet; 50,649; signing for:

Name: Kathleen M. Williams

Registration No.: 34,380

Palmer & Dodge LLP

111 Huntington Avenue

Boston, MA 02199

Tel: 617-293-0100